REMARKS

Claims 1-6, 8, 9, 12-20, and 40-42 have been examined in the Office Action under reply, claims 49-100 having been withdrawn as a result of restriction and claims 7, 10, 11, 21-39, and 43-48 having been withdrawn pursuant to applicants' election of species. With this response, applicants have amended claims 1, 2, 14-16, 20, and 40 and canceled non-elected claims 49-100. Claims 13 and 17-19 have also been canceled herein. Accordingly, claims 1-6, 8, 9, 12, 14-16, 20 and 40-42 are now pending.

The Examiner expanded the search beyond the Applicant's elected species "to capture other polymeric targeted matrix wherein the polymer is of polyethylene glycol or poly(lactic-co-glycolic acid). The claims were thus examined to the extent that they read polyethylene glycol-polycaprolactone copolymers (PEG-PCL), polyethylene glycol (PEG) or poly(lactic-co-glycolic acid) (PLGA) as the polymeric matrix; camptothecin as the bioactive agent; and CRGDC as the targeting ligand."

In the Office Action, the Examiner has rejected the examined claims as follows:

1. Under 35 U.S.C. §112, second paragraph, as indefinite, with respect to use of the term "limited" (claims 13-20);
2. Under 35 U.S.C. §102(b) as anticipated by U.S. Patent No. 5,543,158 to Gref et al. (claims 1-6, 8, 13, 16-17);
3 Under 35 U.S.C. §103(a) as obvious over Gref et al. in view of Quay et al. EP 0727225, Ruoslahti, et al. U.S. Patent No. 5,981,478 and Wallace et al. U.S. Patent No. 5,238,714 (claims 1-6, 16-20, 40-42); and
4. Under 35 U.S.C. §103(a) as obvious over Hunter et al U.S. Patent No. 6,759,431 in view of Domb et al. U.S. Patent No. 5,578,325 and Ruoslahti (claims 1-6, 8-9, 12-20, 40-42).

The rejections are addressed, in part, by the above amendments and are otherwise traversed.

Formal matters:

With regard to the election of species, the Examiner has stated that claims 7, 10, 11, 21-39 and 43-48 are withdrawn as drawn to nonelected species and has requested that a complete

reply to the final rejection must include cancellation of nonelected claims or other appropriate action. (37 CFR 1.144). However, since the present rejection is not final, the withdrawn claims will not be presently cancelled. Pursuant to MPEP 809.02(c) and 37 CFR 1.141, when a generic claim is found to be allowable, Applicants reserve the right to have all species embraced by that generic claim no longer withdrawn from consideration.

Amendments:

Claim 1 has been amended for clarification; the only substantive change made is that the targeting ligand is now specified as a targeting peptide. Support for this amendment is found throughout the specification and most particularly at page 8, line 30; page 30, line 21; and page 31, lines 24-33. Accordingly, claims 17-19 have been canceled and the dependency of claims 20 and 40 has been updated.

Claim 2 has been amended to correct a typographical error regarding the number of oxygen atoms which can bind a sulfur atom.

Claim 13 has been canceled pursuant to the Examiner's objection, and the dependency of claims 14 and 15 has therefore been changed.

Claim 16 has been amended to provide proper antecedent dependency to amended Claim 1.

The Rejection Under 35 U.S.C. §112, second paragraph:

The Examiner has rejected claims 13-20 under 35 U.S.C. §112, second paragraph, with respect to use of the term "limited." As claim 13 has been canceled and the objected-to term is no longer present in these claims, withdrawal of the rejection is in order.

The Rejection Under 35 U.S.C. §102(b) Over Gref et al.:

Claims 1-6, 8, 13, 16-17 have been rejected as anticipated by Gref et al. The Examiner has cited the reference as disclosing compositions comprising particles of a solid biodegradable core comprising PEG and PLGA loaded with a chemotherapeutic or immunosuppressive agent. The Examiner also states that the internal solid core of Gref meets the limitations of the instant matrix, and that as stated in the text at column 12, lines 15-17, "a wide range of biologically active materials and drugs can be incorporated into the polymer at the time of nanoparticle

formation." The Examiner further states that Gref teaches that various types of therapeutic compounds may be incorporated or encapsulated within the biodegradable core and that peptide fragments and/or antibodies can be covalently bounded (sic) to the outside of particles. Finally, the Examiner states that Gref teaches oral or injectable compositions that can be lyophilized. The Examiner asserts that this disclosure anticipates the presently pending claims.

Claims 1-6, 8, 13, 16-17 are distinguishable over the teachings of Gref

To anticipate a claim, the reference must teach every element of the claim. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) Claim 1 has been amended to recite a ....targeting **peptide** covalently bound thereto and an effective amount of a bioactive agent..... Support in the specification for the amendment may be found at page 8, line 30; page 30, line 21; and page 31, lines 24-33. Gref does not teach peptides as targeting ligands. In fact the only reference at all to peptides in Gref is in reference to bioactive substances for delivery, not as targeting ligands. Gref's teaching at column 5, lines 20-30, is for "Fab or Fab_2, antibody fragments...." These fragments not only have a different functional definition from the genus of peptides, structurally they are *glycosylated* fragments; see for example Youings, et al., Biochem. J. (1996) 314;621-630, and therefore cannot properly be used as a teaching of the genus of peptides as targeting ligands in Gref.

Amended claim 1 is now distinguishable over Gref, and withdrawal of the rejection is respectfully requested.

The Rejection Under 35 U.S.C. §103(a) over Gref et al. in View of Quay, Ruoslahti and Wallace:

Claims 1-6, 16-20, 40-42 have been rejected over Gref et al. in view of Quay, et al., Ruoslahti et al. and Wallace et al. The Examiner cites Gref et al., as discussed above, and acknowledges that the reference does not teach the instant targeting ligand, CRDG (sic). The Examiner cites Quay as teaching that various ligands can be conjugated to contrast agents in colloidal dispersions, including CAM ligands such as RGD or cyclic molecules including CRGD. The Examiner cites Ruoslahti for the teaching of specific targeting ligands such as CRGDC as more specific than RGD in inhibiting fibronectin attachment to $\alpha_5\beta_1$. The Examiner states that Wallace teaches [a] process of conjugating amino acid *esters* to the surface of polymers of microcapsules to provide targeting to specific tissue cells, which microcapsules can

be made of PCL or polylactide. The Examiner concludes that the combined teaching of these references renders the subject matter of the pending claims obvious. Applicants respectfully disagree.

Prima Facie Obviousness is not Established Unless There is a Basis in the Art for Combining or Modifying References

Absent some teaching, suggestion or incentive supporting the combination, obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention. *In re Geiger,* 815 F.2d 688, 2 USPQ2d 1278 (Fed. Cir. 1987). Further, the mere fact references can be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, USPQ2d 1430 (Fed. Cir. 1990). In the instant case, the selected art lacks the essential motivation or suggestion to make the claimed invention in light of its teachings. *In re Brower*, 77 F.3d 422, 425, 37 USPQ2d 1633, 1666 (Fed. Cir. 1996).

Claims 1-6, 16-20, 40-42 are not obvious over Gref et al. in view of Quay, et al., Ruoslahti et al. and Wallace et al.

As stated previously, Gref does not teach peptides as targeting ligands for his injectable microparticles. Quay does teach peptide ligand conjugates for use as contrast agents in colloidal dispersions. However, there is no disclosure or suggestion in Quay that the peptide ligand conjugates can be used to formulate the compositions of the claimed invention -- vehicles for the delivery of bioactive agents. The physical and chemical features and properties which render a composition suitable for enhancement of ultrasound contrast are not related to the art of drug delivery nor do they provide motivation for one of skilled in the art to expect success in use as a drug delivery vehicle.

Ruoslahti's teaching of specific targeting ligands based on the RGD motif which have increased binding affinity for fibronectin receptors in no way suggests how the ligands could be incorporated into drug delivery vehicles nor would the teachings motivate one of skill in the art to prepare a vehicle for the delivery of bioactive agents. Finally, the teachings in Wallace are especially inapplicable since the conjugation of amino acid esters to alter the chemistry and structure of end groups of polycaprolactone (PCL) or polylactide is unrelated to the preparation or use of a conjugated *peptide.* Wallace describes how phenylalanine-conjugated polylactide microcapsules demonstrate faster liver uptake than polylactide microcapsules which are not

conjugated. This effect is not correlated with any ligand-receptor interaction and may be due to a masking of surface charge on the microcapsule. In any event, the teachings of Wallace are completely unrelated to the compositions of the claimed invention. Since Wallace's teachings are not related to peptide conjugates, they could not be used as motivation to combine with the other references to teach the claimed invention.

The claims as currently presented are nonobvious over Gref et al. in view of Quay, et al., Ruoslahti et al. and Wallace et al. and withdrawal of the rejection is respectfully requested.

The Rejection Under 35 U.S.C. §103(a) over Hunter et al in View of Domb et al and Ruoslahti:

Claims 1-6, 8-9, 12-20, 40-42 have been rejected over Hunter et al. in view of Domb et al. and Ruoslahti. The Examiner states that Hunter teaches various polymeric drug delivery systems for the delivery of camptothecin, including drug-loaded microspheres or polymeric pastes, comprising PCL, PEG or copolymers thereof and further that the type and concentration of the polymeric carrier can be fashioned to desired release characteristics. The Examiner alleges that Hunter teaches targeted drug delivery, while acknowledging that the use of CRGDC is not specifically taught. The Examiner states that Domb teaches that polymeric moieties of PCL or PEG diblock copolymers can be covalently attached to a targeting ligand to enhance tissue specificity. The teaching of Ruoslahti is the same as recited in the previous section. The Examiner concludes that the combined teaching of these references renders the subject matter of the pending claims obvious. Applicants respectfully disagree.

Prima Facie Obviousness is not Established Unless There is a Basis in the Art for Combining or Modifying References

Absent some teaching, suggestion or incentive supporting the combination, obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention. *In re Geiger,* 815 F.2d 688, 2 USPQ2d 1278 (Fed. Cir. 1987). As with the previously discussed rejection under 35 U.S.C. §103(a), the mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, USPQ2d 1430 (Fed. Cir. 1990). In the instant case, the selected art lacks the essential motivation or suggestion to make the claimed invention in light of its teachings. *In re Brower*, 77 F.3d 422, 425, 37 USPQ2d 1633, 1666 (Fed. Cir. 1996).

Claims 1-6, 8-9, 12-20, 40-42 are not obvious over Hunter et al. in view of Domb et al. and Ruoslahti.

Hunter's use of the term "targeting" contrasts significantly with that defined in the claimed invention. Specifically there is no molecular level interaction disclosed for the delivery of drug to target tissue in Hunter. Hunter's targeting of drugs refers to manually placing the polymeric paste containing the therapeutic agent in the proximity of the target tissue. Hunter's specification reads as follows from column 35, lines 11-20:

"Nanopaste is a suspension of microspheres suspended in a hydrophilic gel. Within one aspect of the invention, the gel or paste can be ***smeared over tissue as a method of locating drug loaded microspheres close to the target tissue.*** Being water based, the paste will soon become diluted with bodily fluids causing a decrease in the stickiness of the paste and a tendency of the microspheres to be deposited on nearby tissue. ***A pool of microsphere encapsulated drug is thereby located close to the target tissue."***

This disclosure does not teach ligand-receptor targeting of the claimed invention nor does it suggest a method of drug delivery which would motivate one of skill in the art to use the teaching of the secondary references (discussed below) to practice the claimed invention. Furthermore, not only does Hunter not teach the use of CRGDC as acknowledged by the Examiner, there is no teaching of the use of any targeting ligands.

The teaching of Domb regarding the covalent attachment of targeting ligands to diblock copolymers does not enumerate peptides among the selected molecules acting as ligands. Rather, the only mention of peptides in Domb is in reference to bioactive materials to be delivered. Since the instant claims as currently amended recite that a targeting ligand comprise a peptide, the Domb reference provides no motivation to combine its teaching with the tissue-proximity nanopaste of Hunter to deliver peptides. As detailed previously, Ruoslahti's teaches specific targeting ligands based on the RGD motif which have increased binding affinity for fibronectin receptors. There is no indication that the method of application of the nanopaste taught by Hunter would allow the drug-loaded microspheres to access the fibronectin receptors which are the intended targets of Ruoslahti's peptides. Indeed, fibronectin receptors are generally associated with the endothelium lining the lumen of the vasculature, and therefore not predictively accessible to the method of "targeting" taught by Hunter. In conclusion, since Domb does not teach peptides as targeting ligands, there would be no motivation to combine Domb with Ruoslahti, and since Hunter's system of drug delivery does not involve targeted

access of internal-tissue receptors for Ruoslahti's peptide ligands, there would be no expectation of success for one of skill in the art to combine Ruoslahti and Hunter to produce the claimed invention.

The claims as currently presented are nonobvious over Hunter et al. in view of Domb, et al. and Ruoslahti et al. and withdrawal of the rejection is respectfully requested.

Conclusion

For the foregoing reasons, applicants submit that the pending claims are patentable over the art and satisfy the requirements of 35 U.S.C. §112. A Notice of Allowance is requested, and a prompt notification thereof would be much appreciated.

If the Examiner has any questions concerning this communication, please contact the undersigned agent at (650) 330-0900.

Respectfully submitted,

By: David A. Sadewasser
David A. Sadewasser
Registration No. 55,587

REED IP LAW GROUP
800 Menlo Avenue, Suite 210
Menlo Park, California 94025
(650) 330-0900 Telephone
(650) 330-0980 Facsimile

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